

**Efficacy and safety of aprepitant in combination with dexamethasone,  
granisetron and metoclopramide as a prophylaxis of chemotherapy induced  
nausea and vomiting in highly emetogenic chemotherapy**

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**INYUVESI  
YAKWAZULU-NATALI**

Submitted as the dissertation component in partial fulfilment for the degree of  
Master of Health Sciences in the school of Health Sciences, University of  
KwaZulu-Natal.

***Supervisor***

Dr Frasia Oosthuizen

**Date submitted: January 2017**

## **PREFACE**

This dissertation is presented in an article format. The findings of the study are presented in chapter 2 in manuscript format as required by the regulations of the University of KwaZulu-Natal. The manuscript will be submitted for publication in the The Cancer Journal.

The journal instructions to the author can be viewed with the following link:

<http://edmgr.ovid.com/ppo/accounts/ifaauth.htm>

The reference list is cited according to the instructions for authors as required by the ICMJE. A complete reference list is included at the end of every chapter and according to the reference style of the University of KwaZulu-Natal.

The dissertation consists of three chapters as follows:

- Chapter 1: provides an introduction to the study as well as the aims, objectives and a brief overview of the methodology.
- Chapter 2: consists of the results, discussion and conclusion written in manuscript format.
- Chapter 3: provides the general conclusions, recommendations, limitations and strengths of the study.

## **ABSTRACT**

### **PURPOSE:**

This study was conducted to evaluate and compare the efficacy and safety of aprepitant in combination with dexamethasone, granisetron and metoclopramide (APR-DGM) versus a treatment regimen containing dexamethasone, granisetron and metoclopramide (DGM) as a prophylaxis in chemotherapy induced nausea and vomiting (CINV) in highly emetogenic chemotherapy in cancer patients.

### **METHODS:**

A retrospective study, conducted in King Abdul-Aziz Medical city (Eastern Region, Saudi Arabia).

Three hundred and nine patients, treated with highly emetogenic chemotherapy, were enrolled in a retrospective, single-center cohort study. This study is a cross sectional study for the period 2010-2014. The primary efficacy endpoint was the complete response (CR) for acute emesis (during the 0–24-hrs. interval after chemotherapy). Secondary endpoint was the CR rates for delayed emesis (during the 24 hrs. -120 hrs. after chemotherapy).

### **RESULTS:**

The APR-DGM regimen showed a significantly improved control in the management of CINV in patients treated with highly emetogenic chemotherapy in acute emesis compared to the DGM regimen ( $P= 0.0021$ ). No significant difference was observed between the two regimens with regards to delayed emesis ( $P= 0.145$ ). Both groups were tolerated well, and the rates of adverse events were not significantly different between groups.

### **DISCUSSION:**

The addition of aprepitant to the standard regimen of dexamethasone, granisetron and metoclopramide was found to be significantly better than dexamethasone, granisetron and metoclopramide alone in the control of acute emesis, but with no significant change in delayed emesis. This study therefore supports the change of regimen in the management of acute emesis with highly emetogenic chemotherapy to include aprepitant.

**Keywords:** aprepitant. CINV, nausea, vomiting, safety, efficacy

## DECLARATION 1 - PLAGIARISM

**I, Iman Moustafa**, declare that:

1. The research reported in this thesis, except where otherwise indicated, and is my original work.
2. The work described in this dissertation has not been submitted for any degree or examination at any other university.
3. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:
  - a) Their words have been re-written but the general information attributed to them has been referenced.
  - b) Where their exact words have been used, then their writing has been placed inside quotation marks, and referenced.
4. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the reference sections.

Signed:



Name: Iman Moustafa

Date \_\_\_\_\_

This is to certify that the contents of this thesis are the original work of Iman Moustafa and as the candidate's supervisor; I have approved this thesis for submission.

1. Signed: \_\_\_\_\_ Name: Dr. Frasia Oosthuizen Date: \_\_\_\_\_

## **DECLARATION 2 – ETHICS APPROVAL**

This study received approval from the Investigational Review Board KAIMRC Research Office - King Abdullah International Medical Research Center under Subject RA15/002/A - "Efficacy and safety of Aprepitant as a prophylaxis of CINV in highly emetogenic level of chemotherapy in combination with Dexamethasone, Granisetron and Metoclopramide (DGM)". (Annexure 1).

Full ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE050/16). (Annexure 2).

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

### **DECLARATION 3 – MANUSCRIPT PUBLICATION**

1. My contribution to the project was as follows:

Iman Moustafa: Principle Investigator – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of dissertation.

2. The contributions of others to the project were as follows:

Dr Frasia Oosthuizen: Supervisor – supervision of the concept of the study and review of the dissertation and manuscript.

## **DEDICATION**

Every challenging work needs self-efforts as well as the blessings of God and the guidance of elders, especially those who are very close to our hearts. I dedicate this thesis and give special thanks to my dad, sisters, and my family for their continuous love and support throughout my studies and special thank for my husband for his support. I will always appreciate all that you have done.



## ACKNOWLEDGEMENTS

I would like to extend my sincerest gratitude to my supervisor Dr Frasia Oosthuizen for her continued support and mentorship while completing my thesis. I am incredibly grateful for her ongoing encouragement and the many learning opportunities provided to me while completing my Masters requirements.

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A lot of thanks to my lovely husband Dr. Bawdy Essam, my sons Mostafa, Omar and my lovely daughter Leena and all my family for supporting me mentally and emotionally and for being my pillar of strength. Special thanks to Mr. Abdulkrim Cara and Mr. Dossary Ibrahim for their support. Without your encouragement and dedication to assist me, this dissertation would not have been possible.

I would like to thank my loved ones for their unfailing patience and motivation throughout the entire process. My profound appreciation goes out to you all.

## LIST OF ACRONYMS AND ABBREVIATIONS

<b>ABVD</b>	Doxorubicin , Bleomycin, Vinblastine and Dacarbazine
<b>AC</b>	doxorubicin and cyclophosphamide
<b>ASCO</b>	American Society of Clinical Oncology
<b>APR</b>	Aprepitant
<b>APR-DGM</b>	Aprepitant, Dexamethasone, Granisetron and Metoclopramide
<b>ADE</b>	Adverse Drug Event
<b>CAF</b>	doxorubicin, cyclophosphamide, and fluorouracil
<b>CEF</b>	cyclophosphamide, epirubicin and fluorouracil
<b>CINV</b>	Chemotherapy Induced Nausea and Vomiting
<b>CR</b>	Complete Response
<b>DGM</b>	Dexamethasone, Granisetron and Metoclopramide
<b>ECOG</b>	Eastern Cooperative Oncology Group
<b>ESMO</b>	European Society for Medical Oncology
<b>HL</b>	Hodgkin Lymphoma

<b>MASCC</b>	Multinational Association for Supportive Care in Cancer
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NCI</b>	National Cancer Institute
<b>NHL</b>	(Non Hodgkin Lymphoma)
<b>RCHOP</b>	Rituximab , Doxorubicin , Cyclophosphamide , Vincristine, Prednisone or Methylprednisolone
<b>SRS</b>	Safety Reporting System
<b>UKZN</b>	University of KwaZulu-Natal
<b>WHO</b>	World Health Organization

## **LIST OF TABLES**

Table 1: Schedule of doses in DGM regimen	page 27
Table 2: Schedule of doses in APR-DGM regimen	page 28
Table 3: Univariate analysis for early and late emesis per each group	page 30
Table 4: Adverse events	page 32

## TABLE OF CONTENTS

<u>CONTENT</u>	<u>PAGE NO.</u>
PREFACE.....	1
ABSTRACT .....	2
DECLARATION 1 – PLAGIARISM.....	4
DECLARATION 2 – ETHICS APPROVAL .....	5
DECLARATION 3 – MANUSCRIPT.....	6
DEDICATION .....	7
ACKNOWLEDGEMENTS .....	8
LIST OF ACRONYMS AND ABBREVIATIONS.....	9
LIST OF TABLES .....	11
 CHAPTER 1	
INTRODUCTION .....	15
1.1. Background and rationale for this study .....	15
1.2. Research questions.....	16
1.3. Aims and objectives.....	16
1.4. Significance of the study.....	17
1.5. Research Methodology.....	18
1.5.1 Study design.....	18
1.5.2 Data source .....	19
1.5.3 Data analysis .....	20
1.5.4 Data management.....	20
1.5.5 Ethical approval.....	20
1.6 Chapter summary .....	21
References .....	21
 CHAPTER 2	
2. MANUSCRIPT FOR SUBMISSION AND PUBLICATION	
2.1 Introduction.....	23

2.2 Manuscript .....	24
References.....	38

### CHAPTER 3

3. CONCLUSIONS.....	40
3.1 Introduction .....	40
3.2 Strengths of the study methodology and sign.....	40
3.3 Conclusions drawn from the study findings.....	40
3.4 Significance of the study .....	41
3.5 Limitations of the study.....	41
3.6 Recommendations .....	42
3.7 Chapter summary .....	43
References .....	43

### ANNEXURES .....

ANNEXURE 1 – Ethical approval letter obtained from the University of KwaZulu-Natal

ANNEXURE 2 – Ethical approval letter obtained from KAIMRC Research Office - King Abdullah International Medical Research Center



## **CHAPTER 1**

### **1. INTRODUCTION**

According to the world statistics, 14.1 million adults in the world were diagnosed with cancer in 2012 and 8.2 million deaths resulted from cancer in the world in the same year.<sup>1</sup> Therefore a lot of research is directed towards the treatment of cancer and the management of related side effects of chemotherapy. Although there are many side effects associated with chemotherapy, chemotherapy-induced nausea and vomiting (CINV) is considered an extreme side effect that affects the quality of life of the patient.<sup>2</sup>

#### **1.1 Background and rationale for this study**

CINV is one of the greatest sources of distress for patients. Because severe CINV may force interruption of chemotherapy, it is important to control CINV to achieve successful chemotherapy. Emesis are classified according to the two following major types: 1) acute emesis is vomiting that occurs during the first 18-24 hours after chemotherapy administration with peak occurring at 4 - 6 hours depending on the agent given and 2) delayed emesis with vomiting occurring > 18-24 hours after chemotherapy administration, but may occur up to 5 days after chemotherapy with the peak in 2 to 3 days.<sup>3</sup> CINV can range from mild, to moderate and severe.<sup>4</sup>

In patients treated with highly emetogenic chemotherapy, 60% experience delayed nausea, and 50% experience delayed emesis. In patients treated with moderately emetogenic chemotherapy, 52% experience delayed nausea, and 28% experience delayed emesis.<sup>4</sup> At the 2009 MASCC / ESMO Consensus Conference, an expert panel used data to establish rankings of emetogenicity for chemotherapy agents.<sup>5</sup> Oral chemotherapy agents are now ranked separately from IV agents as there are intrinsic differences in emetogenicity as well as different schedules of administration.<sup>6,7</sup>



The most problematic effects caused by CINV are dehydration, malnutrition, metabolic imbalances, and potential withdrawal from future cycles of chemotherapy.

## **1.2 Research questions**

This study will determine the efficacy and safety of aprepitant by comparing two treatment regimens for prophylaxis of CINV:

**Regimen 1:** patients treated with the antiemetic regimen **DGM** containing Dexamethasone (D), Granisetron (G) and Metoclopramide (M).

**Regimen 2:** patients treated with **APR –DGM** containing Aprepitant (APR), Dexamethasone (D), Granisetron (G) and Metoclopramide (M).

## **1.3 Aims and objectives for this study**

The aim of this study is to determine if aprepitant is safe and effective by comparing aprepitant in combination with DGM as a prophylaxis of CINV to the DGM regimen (without aprepitant) as prophylaxis of CINV in highly emetogenic chemotherapy .

### **Objectives of the study:**

#### **Primary objectives**

##### ***1-Efficacy of aprepitant:***

The primary end point is to evaluate the acute emesis within 24 hours after administration of chemotherapy (0-24 hours) by using complete response (CR): no emesis, no admission because of emesis and no rescue therapy needed.

Efficacy of aprepitant will be determined by comparing the incidence of acute emesis (0-24 hr.) in regimen 1 (DGM) vs regimen 2 (APR-DGM) via the following:

- a) Cases with emesis.
- b) Administration of antiemetic rescue medication including metoclopramide, lorazepam, granisetron or dexamethasone.
- c) Hospital admissions due to CINV

### ***2-Safety of the aprepitant:***

Determine the observed adverse drug events in the regimen 1 (DGM) compared to regimen 2 (APR-DGM).

### **The secondary objective:**

The secondary end point is the proportion of patients with a complete response (CR), no emesis or use of rescue therapy, after the administration of chemotherapy in delayed (24 -120 hours) phase of emesis.

1-Evaluate the incidence of delayed emesis (25-120 hours) in regimen 1 (DGM) 25-120 hours after administration of chemotherapy compared to regimen 2 (APR-DGM) 25-120 hours after administration of chemotherapy.

### **1.4 Significance and Novelty of the study:**

The efficacy and safety of aprepitant added to dexamethasone, metoclopramide and granisetron have not been studied before as most studies included aprepitant added to dexamethasone and 5HT3 antagonists e.g. granisetron only, without using metoclopramide.

Most of retrospective studies have been done on cisplatin and anthracycline; this study will be an exploratory retrospective study assessing the efficacy and safety of aprepitant with a chemotherapy regimen containing doxorubicin and cyclophosphamide amongst Arabic people.

## 1.5 Research Methodology

### 1.5.1 Study design

This study was designed as a retrospective medical chart review, analytic, single-center study using 309 patients, conducted at National Guard Hospital in King Abdul-Aziz Medical city (Eastern Region, Saudi Arabia).

The study population consisted of cancer patients treated with a highly emetogenic regimen containing 1) anthracycline like doxorubicin, epirubicin and cyclophosphamide as treatment for breast cancer and NHL (Non Hodgkin Lymphoma), and 2) dacarbazine in HL (Hodgkin Lymphoma) in the period from April 2010 till the end of 2014.

The chemotherapy regimens used were:

#### Breast cancer protocols

1- AC: intravenous doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>, CAF: intravenous doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and fluorouracil 500 mg/m<sup>2</sup>.

2- CEF: intravenous epirubicin 100 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and fluorouracil 500 mg/m<sup>2</sup>.

#### Lymphoma protocols

3- RCHOP (Rituximab 375 mg/m<sup>2</sup> Doxorubicin 50 mg/m<sup>2</sup> Cyclophosphamide 750 mg/m<sup>2</sup> Vincristine 1.4mg/m<sup>2</sup>, Prednisone 45 mg/m<sup>2</sup> PO or Methylprednisolone 125 mg IV ).

4- ABVD (. Doxorubicin 25 mg/m<sup>2</sup> Vinblastine 6 mg/m<sup>2</sup> Bleomycin 10 mg/m<sup>2</sup> Dacarbazine 375 mg/m<sup>2</sup>).

These protocols have high risk of emesis and cause nausea and vomiting in more than 90% of oncology patients and the frequency of emesis is more than three times a day. <sup>4</sup>

### 1.5.2 Data source

Data was extracted from electronic charts and nurse's notes for 308 patients - 156 in DGM group and 153 APR-DGM group. Data was reviewed by one reviewer and verified by an additional reviewer. All data was collected in Excel and contained all variables including demographic data such as age, nationality, race, gender, surface area and performance of the patient according to ECOG, and clinical characteristics like type of cancer, name of protocols and number of courses taken.

To measure CR, the data collected included early emesis, late emesis, use of rescue medication (acute phase and early phase) and number of hospital admission.

Review of the patient file and safety reporting system (SRS) were used to extract all information related to adverse event(s), drug-related adverse event(s), or serious adverse event(s). National Cancer Institute (NCI) toxicity criteria (version 3.0) were used to assign toxicity grades.

### 1.5.3 Data analysis

The primary objective was to determine efficacy of aprepitant by evaluating the incidence of acute emesis (0-24 hr.) in both treatment groups. The primary end point was the proportion of patients with a complete response (no emesis, no admission or use of rescue therapy) after the administration of chemotherapy in 0–24-hours.

The second primary objective was to determine the safety of the aprepitant. This was done by evaluating the incidence of delayed emesis (25-120 hours) in both treatment groups.

300 patients were required to achieve 80% statistical power by using two Independent Proportions (Null Case) Power Analysis. The test statistic used was the two-sided Z test with continuity correction and unpooled variance. The significance level of the test was targeted at 0.05. Baseline patient demographics and clinical characteristics as well as safety data were summarized using descriptive statistics. Descriptive summary statistics are presented for each of the efficacy

parameters. Chi square tests of independence were performed on nominal variables and used to determine the CR. All statistical tests were two-sided, and  $p < 0.05$  was considered significant. Data was coded and analysis into SPSS for statistical analysis IBM SPSS software version, 20.

#### 1.5.4 Data Management

Data was collected from the patient medical records and electronic system. Raw data was imported in Excel. The primary investigator requested access to use and extract data as per the policy of the institution.

#### 1.5.5 Ethical approval

Full ethical approval for the study was obtained from the Humanities and Social Sciences Research Ethics Committee of the University of KwaZulu-Natal (REC-290408-009) 6 May 2016 – (Annexure 1), and from the Investigational Review Board KAIMRC Research Office - King Abdullah International Medical Research Center under Subject RA15/002/A - "Efficacy and safety of Aprepitant as a prophylaxis of CINV in highly emetogenic level of chemotherapy in combination with Dexamethasone, Granisetron and Metoclopramide (DGM)".

No patient hospital numbers, names/surnames/initials/ or date of birth/identification numbers were reported in the data sets, hence, patient confidentiality was maintained at all times.

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

### 1.6 Chapter summary

This chapter provided a background and rationale of the study. It also included the aims, objectives, research questions and a brief overview of the methodology.

## References

1. Ferlay, J., Soerjomataram, I., Ervik, M. & others. GLOBOCAN 2012 v1. 0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet], International Agency for Research on Cancer, 2013. *globocan. iarc. fr/*. Accessed **11**, (2013).
2. Hesketh, P. J., Aapro, M., Street, J. C. & Carides, A. D. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Support. care cancer* **18**, 1171–1177 (2010).
3. Network, N. C. C. & others. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): antiemesis. Version 2.2014. April 18, 2014. (2015).
4. Clinical, N., Guidelines, P. & Guidelines, N. Antiemesis. (2016).
5. Roila, F. *et al.* Guideline update for MASCC and ESMO in the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann. Oncol.* **21**, v232--v243 (2010).
6. Grunberg, S. M. *et al.* Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer* **100**, 2261–2668 (2004).
7. Kris, M. G. *et al.* American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J. Clin. Oncol.* **24**, 2932–2947 (2006).
8. Hesketh, P. J. *et al.* Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J. Clin. Oncol.* JCO--2015 (2015). doi:10.1200/JCO.2015.64.3635
9. Ettinger, D. S. *et al.* Antiemesis. *J. Natl. Compr. Cancer Netw.* **10**, 456–485 (2012).
10. Recommendations, F. O ncologist. 1143–1150 (2007). doi:10.1634/theoncologist.12-9-1143
11. Herrstedt, J. J. J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. *Nat Clin Pr. Oncol* **5**, 32–43 (2008).
12. Carlson, R. W. *et al.* NCCN practice guidelines for breast cancer. *Oncol. (willist. Park. NY)* **14**, 33–49 (2000).
13. Zelenetz, A. D. Guidelines for NHL: updates to the management of diffuse large B-cell lymphoma and new guidelines for primary cutaneous CD30+ T-cell lymphoproliferative disorders and T-cell large granular lymphocytic leukemia. *J. Natl. Compr. Cancer Netw.*

- 12**, 797–800 (2014).
14. Hoppe, R. T. *et al.* Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. *J. Natl. Compr. Cancer Netw.* **10**, 589–597 (2012).
  15. Hornby, P. J. Central neurocircuitry associated with emesis. *Am. J. Med.* **111**, 106–112 (2001).
  16. Rojas, C. & Slusher, B. S. Pharmacological mechanisms of 5-HT<sub>3</sub> and tachykinin NK<sub>1</sub> receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur. J. Pharmacol.* **684**, 1–7 (2012).
  17. Hesketh, P. J. Chemotherapy-Induced Nausea and Vomiting. (2008).
  18. 8000726 @ [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov). at <<https://www.ncbi.nlm.nih.gov/pubmed/8000726>>
  19. Tavorath, R. & Hesketh, P. Drug Treatment of Chemotherapy-Induced Delayed Emesis. *Drugs* **52**, 639–648 (1996).
  20. Roscoe, J. A. *et al.* Prevention of delayed nausea: a University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. *J. Clin. Oncol.* **30**, 3389–3395 (2012).
  21. Roila, F. *et al.* Delayed emesis: moderately emetogenic chemotherapy. [Review] [21 refs]. *Support. Care Cancer* 104–108 (2005). doi:10.1007/s00520-004-0700-8
  22. Bender, C. M. *et al.* Nausea and Vomiting. 94–103 (2002).
  23. Hesketh, P. J., Aapro, M., Street, J. C. & Carides, A. D. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment : analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. 1171–1177 (2010). doi:10.1007/s00520-009-0737-9
  24. Kris, M. G. Delayed emesis following anticancer chemotherapy 8000726 @ [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov). *SUPPORT CARE CANCER* (1994). at <<https://www.ncbi.nlm.nih.gov/pubmed/8000726#>>

## Chapter 2

### 2. MANUSCRIPT FOR SUBMISSION AND PUBLICATION

#### 2.1 Introduction

This chapter describes the general findings and discussion of the results of the study and is represented in the form of a manuscript titled “Efficacy and safety of aprepitant in combination with dexamethasone, granisetron and metoclopramide as prophylaxis for chemotherapy-induced nausea and vomiting” This manuscript will be submitted to the “The Cancer Journal” for publication.

<http://www.ICMJE.org>.

The journal instructions to the author can be viewed with the following link:

<http://edmgr.ovid.com/ppo/accounts/ifaauth.htm>



## **Manuscript**

### **Efficacy and safety of aprepitant in combination with dexamethasone, granisetron and metoclopramide as a prophylaxis of chemotherapy-induced nausea and vomiting**

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## **Abstract**

### **PURPOSE:**

This study was conducted to evaluate and compare the efficacy and safety of aprepitant in a treatment regimen containing aprepitant in combination with dexamethasone, granisetron and metoclopramide (APR-DGM) versus a regimen containing dexamethasone, granisetron and metoclopramide (DGM) only as a prophylaxis in chemotherapy induced nausea and vomiting (CINV) in highly emetogenic chemotherapy in cancer patients.

### **METHODS:**

Three hundred and nine patients, treated with highly emetogenic chemotherapy, were enrolled in a retrospective, single-center cohort study to investigate the efficacy and safety of aprepitant in combination with dexamethasone, granisetron and metoclopramide (APR-DGM) compared to dexamethasone, granisetron and metoclopramide (DGM) without aprepitant. This study is a cross sectional study for the period 2010-2014. The primary efficacy endpoint was the complete response (CR) for acute emesis (during the 0–24-hrs. interval after chemotherapy). Secondary endpoint was the CR rates for delayed emesis (during the 24 hrs. -120 hrs. after chemotherapy).

### **RESULTS:**

The APR-DGM regimen showed a significantly improved control in the management of CINV in patients treated with highly emetogenic chemotherapy in acute emesis compared to the DGM regimen ( $P= 0.0021$ ). No significant difference was observed between the two regimens with regards to delayed emesis ( $P= 0.145$ ). Both regimens were well tolerated, and the rates of adverse events were not significantly different between the regimens.

**DISCUSSION:**

The addition of aprepitant to the standard regimen of dexamethasone, granisetron and metoclopramide was found to be significantly better than dexamethasone, granisetron and metoclopramide alone, but only in the control of acute emesis, with no significant change in delayed emesis. This study therefore supports the change of regimen in the management of acute with highly emetogenic chemotherapy to include aprepitant.

**Keywords:** aprepitant, chemotherapy, nausea, vomiting, safety, efficacy

## **Introduction**

CINV is a common adverse event in cancer therapy. Because CINV has a strong negative influence on patient quality of life (QOL), CINV management is highly important.

Chemotherapeutic agents are generally classified by their emetogenic effects, namely, “highly emetogenic chemotherapy” (HEC), “moderately emetogenic chemotherapy” (MEC), and “lower-minimal emetogenic chemotherapy”, according to the frequency and strength of vomit-inducing effects.<sup>8,9</sup>

The triple antiemetic therapy, using a 5-HT<sub>3</sub> receptor antagonist, dexamethasone, and a neurokinin-1 (NK1) receptor antagonist, is the established and recommended treatment for HEC regimens. This triple antiemetic therapy prevents vomiting, and, to a lesser extent, nausea in the majority of patients.<sup>3,10,11</sup>

While the majority of trials in literature have studied triple medication including dexamethasone, granisetron and aprepitant for prophylaxis of CINV, the aim of this study was to compare aprepitant in combination with DGM as a prophylaxis of CINV to the DGM regimen (without aprepitant) as prophylaxis of CINV in highly emetogenic chemotherapy

## **Method**

### **Study design**

This study was designed as a retrospective medical chart review, single-center study, conducted at the National Guard Hospital in King Abdul-Aziz Medical city (Eastern Region, Saudi Arabia). The study population consisted of cancer patients treated with a highly emetogenic regimen as treatment for either breast cancer, lymphoma NHL (Non Hodgkin Lymphoma) or HL (Hodgkin Lymphoma), in the period from April 2010 till the end of 2014.

The HEC protocols included:

Breast cancer protocols:

AC: intravenous doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup>

CAF: intravenous doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and fluorouracil 500 mg/m<sup>2</sup>,

CEF: intravenous epirubicin 100 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>, and fluorouracil 500 mg/m<sup>2</sup><sup>12</sup>

Lymphomas protocols:

RCHOP (rituximab 375 mg/m<sup>2</sup> doxorubicin 50 mg/m<sup>2</sup> cyclophosphamide 750 mg/m<sup>2</sup> vincristine 1.4 mg/m<sup>2</sup>, prednisone 45 mg/m<sup>2</sup> PO or methylprednisolone 125 mg IV )<sup>13</sup>

ABVD (doxorubicin 25 mg/m<sup>2</sup> vinblastine 6 mg/m<sup>2</sup> bleomycin 10 mg/m<sup>2</sup> dacarbazine 375 mg/m<sup>2</sup>)<sup>14</sup>

This study received approval from the Investigational Review Board KAIMRC Research Office - King Abdullah International Medical Research Center under Subject RA15/002/A - "Efficacy and safety of Aprepitant as a prophylaxis of CINV in highly emetogenic level of chemotherapy in combination with Dexamethasone, Granisetron and Metoclopramide (DGM)". Full ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE050/1).

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with International Conference on Harmonization, Good Clinical Practices, and all applicable regulatory guidelines.

## **Participants**

309 Subjects were selected for inclusion in the study; this included 156 in group DGM and 153 in group APR-DGM.

### **Inclusion criteria:**

- ☐ Patients aged between 18 to 75 years.
- ☐ Chemotherapy naïve patients (have not received chemotherapy before).
- ☐ Patients diagnosed with breast cancer stage II, III, IV or lymphoma stage II, III, IV .

☐ Patients who failed on standard antiemetic therapy with a 5HT3 antagonist plus dexamethasone for moderately emetogenic regimens.

☐ Patients with performance status Eastern Cooperative Oncology Group (ECOG SCORE) less than 5.

**Exclusion criteria:**

☐ Hypersensitivity to aprepitant/fosaprepitant, polysorbate 80 or any ingredients in the formulation.

☐ Patients on concurrent pimozone or cisapride (aprepitant is a weak to moderate dose-dependent inhibitor of CYP3A4 and therefore contraindicated for use with terfenadine, astemizole cisapride, or pimozone (concurrent use may result in life threatening reactions)).

☐ Chemotherapy regimens with minimal, low, or moderate potential for incidence of emetogenicity.

☐ Pregnant and lactating woman.

☐ Patients with any psychological problems.

☐ Patients with a history of depression .

**Interventions**

DGM treatment group: 156 patient charts for the period April 2010 to April 2012, were selected. The DGM regimen was administered according to Table 1.

DGM-APR treatment group: 153 patient charts for the period May 2012 till the end of year 2014 were selected. The DGM –APR regimen were administered according to Table 2.

**Table 1: Schedule of doses in DGM regimen**

Acute emesis	Delay emesis			
Day 1	Day 2	Day 3	Day 4	Day 5
Dexamethasone 16 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 mins infused over 30 mins Dexamethasone 4 mg PO evening of chemotherapy	Dexamethasone 8 mg PO twice daily	Dexamethasone 8 mg twice daily	Dexamethasone 8 mg twice daily	Dexamethasone 8 mg twice daily
Granisetron 1 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 mins infused over 5 mins	Granisetron 2 mg PO Twice daily	Granisetron 2 mg PO Twice daily	Granisetron 2 mg PO Twice daily	Granisetron 2 mg PO Twice daily
Metoclopramide 10 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 mins infused over 30 mins and every 6 hours	Metoclopramide 10 mg Every 6 hours and PRN	Metoclopramide 10 mg Every 6 hours and PRN	Metoclopramide 10 mg Every 6 hours and PRN	Metoclopramide 10 mg Every 6 hours and PRN

**Table 2: Schedule of doses in APR-DGM regimen**

Acute emesis	Delay emesis		
Day 1	Day 2	Day 3	Day 4

Aprepitant 125 mg Before chemotherapy 45-60 mins	Aprepitant 80 mg	Aprepitant 80 mg	
Dexamethasone 12 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 mins infused over 30 mins	Dexamethasone 8 mg oral once daily	Dexamethasone 8 mg oral once daily	Dexamethasone 8 mg oral once daily
Granisetron 1 mg IV mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 mins infused over 5 mins			
Metoclopramide 10 mg IVB in 50 ml normal 0.9 saline before chemotherapy 30 mins infused over 30 mins	Metoclopramide 10 mg Every 6 hours and PRN	Metoclopramide 10 mg Every 6 hours and PRN	Metoclopramide 10 mg Every 6 hours and PRN

It is important to note that dexamethasone should not be added to a chemotherapeutic regimen that already contains corticosteroids; therefore, in the RCHOP protocol used for treatment of Non Hodgkin Lymphoma, dexamethasone was omitted. Methyl prednisolone 125 mg, as part of RCHOP protocol, can cover acute and delayed emesis.

### **Outcomes and Statistical analysis**

The test statistic used was the two-sided Z test with continuity correction and unpooled variance. The significance level of the test was targeted at 0.05. Baseline patient demographics and clinical characteristics as well as safety data were summarized using descriptive statistics. Descriptive summary statistics are presented for each of the efficacy parameters. Chi square tests of independence were performed on nominal variables and used to determine the CR. All statistical



tests were two-sided, and  $p < 0.05$  was considered significant. All statistical analyses were performed using IBM SPSS software VERSION 20.

## **Results**

### **Sociodemographic characteristics**

A total of 309 patient files were analysed, 156 receiving regimen DGM (50.49%) and 153 receiving regimen APR-DGM (49%). The majority of patients were Arabic 298 (96.44%) and only 11(3.56%) non-Arabic. Most patients were Saudi 290 (93.85%) vs 19 (6.15% non-Saudi).

205 from the 309 cases were female (66.34%). 60% female patients (94/156) were on the DGM regimen, and 71% (111/153) on the APR-DGM regimen. 33.66% male patients (62/156) were on the DGM regimen and 42/153 (27%) on the APR-DGM regimen (table 3).

Patients with surface area equal to 2 were 263 (85.11%) and patient with surface area equal to 1 was 46 (14.89%). Performance statues of the patient according to ECOG score was 267 with 0 score (86.41%), 32 (10.36%) with score 1 and 10 (3.24%) with score 2. The mean age of the population was  $47.3 \pm 4.7$ .

### **EFFICACY**

The results show a statistically significant difference in complete response (no emesis, no admission and no use of rescue therapy) in acute emesis when comparing the two treatment regimens (p-value 0.002). The number of emesis in acute phase was statistically significantly lower in the APR-DGM group compared to the DGM group (p-value 0.0021).

The need for rescue medication was also statistically significantly in acute phase (p-value 0.001). for APR-DGM regimen compared to the DGM regimen

No statistical significant differences between the two regimens were observed in the management of delayed emesis (p-value 0.145). The need for rescue medication when receiving treatment with the two different regimens also showed no statistically significance in the delayed phase (p-value 0.075). The numbers of hospital admission between two groups have been decreased (p-value 0.013). (See table 3).

**Table 3: Univariate analysis for early and late emesis per each group (N =309)**

Characteristics	Early emesis	No early emesis	Chi-square	p-value
Group DGM APR-DGM	25 (75.76) 8 (24.24)	131 (47.46) 145 (52.54)	9.4395	0.0021
Characteristics	Late emesis	No late emesis		p-value
Group DGM APR-DGM	35 (22.43%) 26(16.99%)	121 (77.56%) 127(83.01%)	1.44	0.145
Characteristics	Rescue medication (acute phase)	No rescue medication (acute phase )		P-value
Group DGM APR-DGM	27 8	129 145	11.22	0.001
Characteristics	Rescue medication (delayed phase)	No rescue medication (delayed phase )		P-value
Group DGM APR-DGM	31 19	125 134	6.179	0.075
Characteristics	Admission	No admission		P-value
Group DGM APR-DGM	21 8	135 145	6.156	0.013
Characteristics	DGM	APR-DGM		P-value

CR	93 (59.62%)	116 (75.82%)	9.23	0.002
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### **SAFETY**

Safety and tolerability of the two treatment regimens were assessed and compared through clinical review of safety parameters using Chi-Square. Treatment comparisons were made with respect to the P- value and the proportion of patients who reported one or more adverse event(s), drug-related adverse event(s), or serious adverse event(s).

All side effects observed in both regimens were tolerable and manageable. The rates for frequently observed ADEs were not significantly different between the two regimens. None of the patients experienced severe toxicities. (See table 4)

**Table 4 Adverse events (N = 309)**

Characteristics	N (%)	DGM Group (n=156)	APR-DGM Group(n=153)	P -value
Abdominal pain <i>Yes</i> <i>No</i>	41 (13.27) 268 (86.73)	20 (12.28) 136(78.18)	8 (5.23) 145(94.77)	0.02
Agitation <i>Yes</i> <i>No</i>	23 (7.44) 286 (92.56)	9 (5.77) 147(94.23)	14 (9.15) 139 (90.85)	0.258
Anal burning <i>Yes</i> <i>No</i>	14 (4.53) 295 (95.47)	7 (4.49) 149(95.51)	7 (4.58) 146(95.42)	0.971
Anorexia <i>Yes</i> <i>No</i>	44 (14.24) 265 (85.76)	20 (12.82) 136(87.18)	24 (15.69) 129(84.31)	0.471
Allergic reaction <i>Yes</i> <i>No</i>	9 (2.91) 300 (97.09)	4 (2.56) 152(97.44)	5 (3.27) 148(96.73)	0.713

Back pain <i>Yes</i> <i>No</i>	29 (9.39) 280 (90.61)	13 (8.3) 143(91.67)	22 (14.38) 131(85.62)	0.537
Constipation <i>Yes</i> <i>No</i>	33 (10.86) 276 (89.32)	15 (9.62) 141 (90.38)	2 (1.31) 151 (98.69)	0.541
Convulsion <i>Yes</i> <i>No</i>	16 (5.18) 293 (94.82)	12 (7.69) 144 (92.31)	4 (2.61) 149 (97.39)	0.044
Diarrhea <i>Yes</i> <i>No</i>	29 (9.39) 280 (90.61)	13 (8.3) 143 (91.67)	16 (10.46) 137 (89.54)	0.522
Dysuria <i>Yes</i> <i>No</i>	4 (1.29) 305 (98.71)	2 (1.28) 154 (98.72)	2 (1.31) 151(98.69)	0.984
Fatigue <i>Yes</i> <i>No</i>	37 (11.97) 272 (88.03)	17 (10.90) 139 (89.1)	20 (13.07) 133(86.93)	0.556
Face flushing <i>Yes</i> <i>No</i>	16 (5.18) 293 (94.82)	10 (6.41) 146(93.59)	6 (3.92) 147(96.08)	0.324
Headache <i>Yes</i> <i>No</i>	23 (7.44) 286 (92.56)	10 (6.4) 146(93.59)	13 (8.5) 140(91.5)	0.485
Hiccup <i>Yes</i> <i>No</i>	43 (13.92) 266 (86.08)	20 (12.8) 136(87.18)	23 (15) 130(84.76)	0.574
Insomnia <i>Yes</i> <i>No</i>	23 (7.44) 286 (92.56)	12 (7.69) 144(92.31)	11 (7.19) 142(92.81)	0.866
Tremor <i>Yes</i> <i>No</i>	13 (4.21) 296 (95.79)	5 (3.21) 151(69.79)	8 (5.23) 145(94.77)	0.367
Muscle pain	22 (7.12)	12 (7.69)	10 (6.54)	0.693

<i>Yes</i> <i>No</i>	287 (92.88)	144(92.31)	143(93.46)	
Sweating <i>Yes</i> <i>No</i>	15 (4.85) 294 (95.15)	9 (5.77) 147(49.23)	6(3.85) 147(96.08)	0.450
Vaginal candida <i>Yes</i> <i>No</i>	18 (5.83) 299 (96.76)	13 (8.31) 143(91.78)	5 (3.27) 148(96.73)	0.057
Lacrimal duct obstruction and tearing <i>Yes</i> <i>No</i>	25 (8.09) 284 (91.91)	15 (9.62) 141(90.38)	10 (6.54) 143(93.46)	0.975

## Discussion

This study found that the APR-DGM regimen protected approximately 95% of patients from acute emesis after receiving highly emetogenic chemotherapy and enabled them to avoid the use of rescue therapy. This regimen also decreased the number of hospital admission due to CINV in the acute phase.

The addition of aprepitant to a standard therapy regimen consisting of a granisetron plus dexamethasone and metoclopramide improved the control of CINV associated with highly emetogenic chemotherapy in the acute phase. The aprepitant regimen was generally well tolerated, with adverse events similar to those associated with DGM regimen.

The time course and magnitude of improved control of emesis achieved with aprepitant support the hypothesis that superior control of CINV involves the blockade of substance P-mediated nausea and vomiting. The vomiting center in the medulla called the area postrema contains high concentrations of substance P and its receptor, in addition to other neurotransmitters such as choline, histamine, dopamine, serotonin, and opioids. Their activation stimulates the vomiting reflex. Different emetic pathways exist, and substance P/NK1R appears to be within the final common pathway to regulate

vomiting.<sup>15</sup> Substance P is a member of a group of peptides known as tachykinins; these tachykinins bind to neurokinin-1, 2, and 3 receptors. NK1 receptors are found throughout the central nervous system, including the area postrema and nucleus tractus solitarius and NK1 receptors are also found in the GI tract. Aprepitant mediates the effect of substance P by blocking the neurokinin 1 (NK<sub>1</sub>) receptor.<sup>4,16,17</sup>

In this study, it showed there was no significant difference in the response of DGM versus APR-GM in delayed phase emesis. Delayed vomiting occurs after treatment with many anticancer drugs, but has been most often studied following cisplatin or combinations of cyclophosphamide and anthracyclines. The mechanism of this phenomenon is unknown.<sup>18</sup>

In the treatment of delayed emesis in non-cisplatin chemotherapy, corticosteroids and 5-HT<sub>3</sub> receptor antagonists are considered the most useful agents.<sup>19</sup> Dexamethasone has consistently shown its antiemetic efficacy for delayed emesis induced by cisplatin and non-cisplatin agents, whereas the role of 5-HT<sub>3</sub> antagonists alone remains controversial. Metoclopramide, the dopamine receptor antagonist, has been shown to be as efficacious as 5-HT<sub>3</sub> antagonists when combined with dexamethasone for the prevention of delayed emesis[14]. Corticosteroids have synergistic effect with both serotonin antagonists and metoclopramide<sup>21</sup>.

In conclusion, aprepitant represents an important medical advance that can substantially enhance the supportive care of patients with cancer who receive highly emetogenic chemotherapy in acute phase but little support in delayed phase. The aprepitant regimen was generally well tolerated. Both DGM or APR-DGM can be recommended in delayed phase of emesis, but because of the lower cost of DGM should be chosen as prophylaxis for delayed emesis

## References:

1. Ferlay, J., Soerjomataram, I., Ervik, M. & others. GLOBOCAN 2012 v1. 0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet], International Agency for Research on Cancer, 2013. *globocan. iarc. fr/*. Accessed **11**, (2013).
2. Hesketh, P. J., Aapro, M., Street, J. C. & Carides, A. D. Evaluation of risk factors

- predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Support. care cancer* **18**, 1171–1177 (2010).
3. Network, N. C. C. & others. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): antiemesis. Version 2.2014. April 18, 2014. (2015).
  4. Clinical, N., Guidelines, P. & Guidelines, N. Antiemesis. (2016).
  5. Roila, F. *et al.* Guideline update for MASCC and ESMO in the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann. Oncol.* **21**, v232--v243 (2010).
  6. Grunberg, S. M. *et al.* Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer* **100**, 2261–2668 (2004).
  7. Kris, M. G. *et al.* American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J. Clin. Oncol.* **24**, 2932–2947 (2006).
  8. Hesketh, P. J. *et al.* Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J. Clin. Oncol.* JCO--2015 (2015). doi:10.1200/JCO.2015.64.3635
  9. Ettinger, D. S. *et al.* Antiemesis. *J. Natl. Compr. Cancer Netw.* **10**, 456–485 (2012).
  10. Recommendations, F. O ncologist. 1143–1150 (2007). doi:10.1634/theoncologist.12-9-1143
  11. Herrstedt, J. J. J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. *Nat Clin Pr. Oncol* **5**, 32–43 (2008).
  12. Carlson, R. W. *et al.* NCCN practice guidelines for breast cancer. *Oncol. (willist. Park. NY)* **14**, 33–49 (2000).
  13. Zelenetz, A. D. Guidelines for NHL: updates to the management of diffuse large B-cell lymphoma and new guidelines for primary cutaneous CD30+ T-cell lymphoproliferative disorders and T-cell large granular lymphocytic leukemia. *J. Natl. Compr. Cancer Netw.* **12**, 797–800 (2014).

14. Hoppe, R. T. *et al.* Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. *J. Natl. Compr. Cancer Netw.* **10**, 589–597 (2012).
15. Hornby, P. J. Central neurocircuitry associated with emesis. *Am. J. Med.* **111**, 106–112 (2001).
16. Rojas, C. & Slusher, B. S. Pharmacological mechanisms of 5-HT<sub>3</sub> and tachykinin NK<sub>1</sub> receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur. J. Pharmacol.* **684**, 1–7 (2012).
17. Hesketh, P. J. Chemotherapy-Induced Nausea and Vomiting. (2008).
18. 8000726 @ www.ncbi.nlm.nih.gov. at <<https://www.ncbi.nlm.nih.gov/pubmed/8000726>>
19. Tavorath, R. & Hesketh, P. Drug Treatment of Chemotherapy-Induced Delayed Emesis. *Drugs* **52**, 639–648 (1996).
20. Roscoe, J. A. *et al.* Prevention of delayed nausea: a University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. *J. Clin. Oncol.* **30**, 3389–3395 (2012).
21. Roila, F. *et al.* Delayed emesis: moderately emetogenic chemotherapy. [Review] [21 refs]. *Support. Care Cancer* 104–108 (2005). doi:10.1007/s00520-004-0700-8
22. Bender, C. M. *et al.* Nausea and Vomiting. 94–103 (2002).
23. Hesketh, P. J., Aapro, M., Street, J. C. & Carides, A. D. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment : analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. 1171–1177 (2010). doi:10.1007/s00520-009-0737-9
24. Kris, M. G. Delayed emesis following anticancer chemotherapy 8000726 @ www.ncbi.nlm.nih.gov. *SUPPORT CARE CANCER* (1994). at <<https://www.ncbi.nlm.nih.gov/pubmed/8000726#>>



## **CHAPTER 3**

### **3. CONCLUSIONS**

#### **3.1. Introduction**

This study was carried out to evaluate the safety and efficacy of aprepitant by comparing aprepitant in combination with DGM as a prophylaxis of CINV to the DGM regimen (without aprepitant) in highly emetogenic chemotherapy.

#### **3.2 Strengths of the study methodology and design**

Data collection was cost-effective as the data sets used in the study were obtained from electronic medical records and stored as a Microsoft Excel document. The data was easy to analyze using IBM SPSS Statistics 20, considering that it was quantitative and obtained in the form of an extraction sheet and made available electronically.

#### **3.3 Conclusions drawn from the study findings**

This study determined the efficacy and safety of aprepitant by comparing two treatment regimens for prophylaxis of CINV. The first regimen was the antiemetic regimen DGM containing Dexamethasone (D), Granisetron (G) and Metoclopramide (M). The second regimen was APR – DGM containing Aprepitant (APR), Dexamethasone (D), Granisetron (G) and Metoclopramide (M).

Conclusions drawn from the study findings based on each of these objectives.

The primary objective was to determine the efficacy and safety of aprepitant by comparing the incidence of acute emesis (0-24 hr.) in regimen 1 (DGM) vs regimen 2 (APR-DGM) via the

following a) Cases with emesis; b) Administration of antiemetic rescue medication (Metoclopramide 10-20 mg, Lorazepam, Granisetron or Dexamethasone); c) The hospital admissions due to CINV (chemotherapy induces nausea and vomiting). The APR-DGM regimen showed a significantly improved control in the management of CINV in patients treated with highly emetogenic chemotherapy in acute emesis compared to the DGM regimen ( $P= 0.0021$ ).

Safety of the aprepitant was determined by the observed adverse drug events in the regimen 1 (DGM) compared to regimen 2 (APR-DGM). Both regimens were well tolerated, and the rates of adverse events were not significantly different between the regimens.

The secondary objective was to determine the efficacy of aprepitant in delayed phase of emesis and the secondary end point is the proportion of patients with a complete response (CR; no emesis or use of rescue therapy) after the administration of chemotherapy (25 -120 hours). No significant difference was observed in the management of delayed emesis between the two regimens ( $P= 0.145$ ).

### **3.4 Significance of the study**

The efficacy and safety of aprepitant added to dexamethasone, metoclopramide and granisetron have not been studied before as most studies done included only aprepitant added to dexamethasone and a 5HT3 antagonist e.g. granisetron, without using metoclopramide as a premedication.

All retrospective studies have been done on cisplatin and only one study evaluated aprepitant as CINV for patient treated with an anthracycline containing regimen; there is therefore a lack of knowledge regarding treatment with a aprepitant-containing regimen for AC treatment of cancer.

This study was an exploratory retrospective study assessing the effectiveness and safety of DGM in combination with aprepitant for CINV in highly emetic chemotherapy regimens compared to DHM alone amongst Arabic people.

### **3.5 Limitations of the study**

As data were obtained from patient medical records and not via direct patient interaction, some information was not available.

1- Alcohol consumption is a very important factor and can have an effect on the risk of CINV. Alcoholic consumption can decrease the CINV. This type of information is considered as personal information in the study population, therefore not all patients may be willing to provide accurate information on this type of questions, so the reported information may not precise.<sup>22</sup>

2- If a patient has motion sickness. People with history of motion sickness have high risk for CINV.

3-Patients with depression are more susceptible for emesis than normal persons. Despite excluding these patients some patients included in the study population might still have undiagnosed patients with depression. Cancer itself can affect psychological status of the patients, and can cause depression.

4-Any psychological factor like distress, anxiety can also effect on CINV, and is considered a difficult factor to be evaluated especially because it is a retrospective study.<sup>23</sup>

5-The amount of sleep before the day of chemotherapy can affect CINV, and this factor is considered a very difficult to determine or assess.

6- The sample size is considered small which can affect the power of the study.

### **3.6 Recommendations**

For AC-regimens, both the 5-HT<sub>3</sub> and NK1-sensitive mechanism appear to be important in the initial phase; NK1 effects have the greatest impact with the first 12 hours after chemotherapy .<sup>19,24</sup>.

Using 5HT<sub>3</sub> for covering delay emesis with aprepitant need more study.DGM or APR-DGM can be recommended in delayed phase of emesis, but because of the lower cost of DGM should be chosen as prophylaxis for delayed emesis.

Delayed emesis because of CINV need more studies with different chemotherapy regimens.

Adding metoclopramide with low doses with aprepitant in all phases of chemotherapy needs more study.

### **3.7 Chapter summary**

The final chapter highlighted the conclusions drawn from the findings of the study, described the strengths and limitations of the study, as well as provided recommendations for future research.

## References


1. Ferlay, J., Soerjomataram, I., Ervik, M. & others. GLOBOCAN 2012 v1. 0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet], International Agency for Research on Cancer, 2013. *globocan. iarc. fr/*. Accessed **11**, (2013).
2. Hesketh, P. J., Aapro, M., Street, J. C. & Carides, A. D. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Support. care cancer* **18**, 1171–1177 (2010).
3. Network, N. C. C. & others. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): antiemesis. Version 2.2014. April 18, 2014. (2015).
4. Clinical, N., Guidelines, P. & Guidelines, N. Antiemesis. (2016).
5. Roila, F. *et al.* Guideline update for MASCC and ESMO in the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann. Oncol.* **21**, v232--v243 (2010).
6. Grunberg, S. M. *et al.* Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer* **100**, 2261–2668 (2004).
7. Kris, M. G. *et al.* American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J. Clin. Oncol.* **24**, 2932–2947 (2006).
8. Hesketh, P. J. *et al.* Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J. Clin. Oncol.* JCO--2015 (2015). doi:10.1200/JCO.2015.64.3635
9. Ettinger, D. S. *et al.* Antiemesis. *J. Natl. Compr. Cancer Netw.* **10**, 456–485 (2012).

10. Recommendations, F. Oncologist. 1143–1150 (2007). doi:10.1634/theoncologist.12-9-1143
11. Herrstedt, J. J. J. Antiemetics: an update and the MASCC guidelines applied in clinical practice. *Nat Clin Pr. Oncol* **5**, 32–43 (2008).
12. Carlson, R. W. *et al.* NCCN practice guidelines for breast cancer. *Oncol. (willist. Park. NY)* **14**, 33–49 (2000).
13. Zelenetz, A. D. Guidelines for NHL: updates to the management of diffuse large B-cell lymphoma and new guidelines for primary cutaneous CD30+ T-cell lymphoproliferative disorders and T-cell large granular lymphocytic leukemia. *J. Natl. Compr. Cancer Netw.* **12**, 797–800 (2014).
14. Hoppe, R. T. *et al.* Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. *J. Natl. Compr. Cancer Netw.* **10**, 589–597 (2012).
15. Hornby, P. J. Central neurocircuitry associated with emesis. *Am. J. Med.* **111**, 106–112 (2001).
16. Rojas, C. & Slusher, B. S. Pharmacological mechanisms of 5-HT<sub>3</sub> and tachykinin NK<sub>1</sub> receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur. J. Pharmacol.* **684**, 1–7 (2012).
17. Hesketh, P. J. Chemotherapy-Induced Nausea and Vomiting. (2008).
18. 8000726 @ www.ncbi.nlm.nih.gov. at <<https://www.ncbi.nlm.nih.gov/pubmed/8000726>>
19. Tavorath, R. & Hesketh, P. Drug Treatment of Chemotherapy-Induced Delayed Emesis. *Drugs* **52**, 639–648 (1996).
20. Roscoe, J. A. *et al.* Prevention of delayed nausea: a University of Rochester Cancer Center Community Clinical Oncology Program study of patients receiving chemotherapy. *J. Clin. Oncol.* **30**, 3389–3395 (2012).
21. Roila, F. *et al.* Delayed emesis: moderately emetogenic chemotherapy. [Review] [21 refs]. *Support. Care Cancer* 104–108 (2005). doi:10.1007/s00520-004-0700-8

22. Bender, C. M. *et al.* Nausea and Vomiting. 94–103 (2002).
23. Hesketh, P. J., Aapro, M., Street, J. C. & Carides, A. D. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment : analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. 1171–1177 (2010). doi:10.1007/s00520-009-0737-9
24. Kris, M. G. Delayed emesis following anticancer chemotherapy 8000726 @ [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov). *SUPPORT CARE CANCER* (1994). at <<https://www.ncbi.nlm.nih.gov/pubmed/8000726#>>



## MEMORANDUM

**Sys Reg Num**   
HAS-16-437780-10730

**Memo Date** 19-Jan-2016 / 09-04-1437

**To** Iman Moustafa - Pharmacist I - Pharmacy - Al Ahsa

**Thru** Yusri Taha - Consultant Infectious Diseases - Ma - Medicine - Al Ahsa - ( Approved)

**From** Kaimrc Research Office - King Abdullah International Medical Research Center

**Subject** RA15/002/A - "Efficacy and safety of Aprepitant as a prophylaxis of CINV in highly emetogenic level of chemotherapy in combination with Dexamethasone, Granisetron and Metoclopramide (DGM)"

After careful scientific re-evaluation of the above-mentioned proposal and as per comments and suggestions of the respective reviewer, on behalf of the committee, I am grateful to inform you that your Research Proposal has been finally **approved** and you may begin your data collection upon receipt hereof.

According to policies and procedures since your proposal does not include Ethical/Budget consideration, the Committee would like you to submit the progress of your report in three months' time. You are further requested to submit a report upon completion of the project and final manuscript.

Indeed, I would like to acknowledge your participation chained with efforts and hard works to the research center.

Thank you and best regards,

**CC :** King Abdullah International Research Center Department - King Abdullah International Medical Research Center

06 May 2016

Mrs IMF Moustafa (214564741)  
Discipline of Pharmaceutical Sciences  
School of Health Sciences  
[emooo74@yahoo.com](mailto:emooo74@yahoo.com)

**Protocol:** Efficacy and safety of aprepitant in combination with dexamethasone, granisetron and metoclopramide as a prophylaxis of chemotherapy induces nausea and vomiting in highly emetogenic chemotherapy.

**Degree:** MPharm

**BREC reference number:** BE050/16

The Biomedical Research Ethics Committee has considered and noted your application received on 29 January 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 05 April 2016 to queries raised on 08 March 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval**.

This approval is valid for one year from **06 May 2016**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

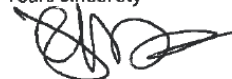
Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **14 June 2016**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely



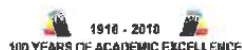
Professor J Tsoka-Gwegweni  
Chair: Biomedical Research Ethics Committee

cc supervisor: [oothuizenf@ukzn.ac.za](mailto:oothuizenf@ukzn.ac.za)  
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Principal Campuses:  Edgewood  Howard College  Medical School  Pietermaritzburg  Westville



